acids 1-1113 of SEQ ID NO:2, said identity being determined by using the WU-BLAST-2.0a19 program and calculating the number of matching identical amino acids divided by the sequence length of SEQ ID NO:2.

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23 (once amended). The isolated nucleic acid molecule of Claim 22 that comprises a nucleic acid sequence having at least 80% sequence identity with nucleotides 1-3419 of SEQ ID NO:1, said identity being determined by using the WU-BLAST-2.0a19 program and calculating the number of matching identical amino acids divided by the sequence length of SEQ ID NO:1.

Please add the following new claims:

34 (new). The *C. elegans* of Claim 1 that has been genetically engineered to express or mis-express SREBP.

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35 (new). The *C. elegans* of Claim 1 that has been genetically engineered to express or mis-express SCAP.

36 (new). The *C. elegans* of Claim 1 that has been genetically engineered to express or mis-express S2P.

REMARKS

The specification has been amended on page 14 in order to correct two typographical errors.

Upon entry of this amendment, claims 1-4, 6, 8-11, 13-18, 22, 23, 25-28 and 34-36 will be pending in the above-captioned application. Claims 5, 7, 12, 19-21, 24 and 29-33 have been canceled without prejudice. Claims 5, 19-21 and 29-33 were canceled in view of their withdrawal from consideration due to a restriction requirement. Applicants reserve the right to prosecute the subject matters of the non-elected claims in one or more related applications.

Claims 1-4, 6, 8-11, 13, 15-18, 22 and 23 have been amended to more particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, claim 1 has been amended to recite a *C. elegans* that has been genetically engineered to express or mis-express an SREBP pathway protein selected from the group consisting of SREBP, SCAP, and S2P, or the progeny of said *C. elegans* that has inherited said SREBP pathway protein expression or mis-expression, wherein said SREBP pathway protein expression or mis-expression results in an intestinal defect phenotype. Support for amended claim 1 is found, *inter alia*, at page 5, lines 26-27 and lines 31-33; page 20, lines 14-17; page 21, line 1; and page 29, lines 28-30.

Claims 2-4, 6 and 8-11 have been amended to specifically recite *C. elegans*. Support for this amendment is found throughout the specification, *inter alia*, at page 5, lines 26-27; page 20, lines 14-17 and Examples 1-5. Claim 2 has also been amended to recite "genetically engineered". Support is found on page 21, line 1. Claim 4 has also been amended to recite "heterologous promoter". Support for the amendment is found on page 12, line 8-35. Claim 8 has also been amended to recite that the SREBP pathway protein is SREBP, and support for this amendment is found at page 5, lines 30-33. Claims 11 and 15 have been amended to recite that the intestinal defect phenotype is a pale intestine phenotype. Support for this amendment is found at page 29, lines 26-30.

Claim 13 has been amended to recite a method for studying lipid metabolism comprising obtaining a first *C. elegans* defined by Claim 1 and a second *C. elegans* that has the same genetic engineering as the first *C. elegans* and that additionally has a mutation in a gene of interest, and detecting a difference between the intestinal defect phenotype of the first *C. elegans* and the intestinal defect phenotype of the second *C. elegans*, wherein a difference in the phenotypes identifies the gene of interest as capable of modifying the function of the gene encoding said SREBP pathway protein. Support for amended claim 13 is found throughout the specification, specifically at page 4, lines 12-14; page 30, line 13 to page 32, line 27. Claim 16 has been amended to recite that the detection step comprises staining the first and second *C. elegans in vivo* with a fluorescently-labelled fatty acid conjugate to measure lipid content within said first and second *C. elegans*. Support is found at page 34, line 9 to page 36, line 4. Claim 17 has been amended to recite the specific fatty acids. Support for amended claim 17 is found at page 34, lines 26-29 in the specification. Claim 18 has been amended to recite a method for studying lipid metabolism comprising administering one or more compounds to a *C. elegans* defined by Claim 1; and observing any changes in lipid content of said *C. elegans*. Support is found at page 34, line 9 to page 36, line 4.

Claim 22 has been amended to recite an isolated nucleic acid molecule of less than 15 kb comprising a nucleic acid sequence that (a) hybridizes to SEQ ID NO:1 under conditions comprising hybridizing in a buffer comprising 6X SSC / 0% formamide at 34°C and washing in a buffer comprising 2X SSC at 45°C, and (b) encodes a functionally active SREBP polypeptide, said polypeptide having at least 80% sequence identity with amino acids 1-1113 of SEQ ID NO:2, said identity being determined by using the WU-BLAST-2.0a19 program and calculating the number of matching identical amino acids divided by the sequence length of SEQ ID NO:2. Support for amended claim 22 is found in

the specification, *inter alia*, at page 6, lines 23-25; page 8, line 13 to page 10, line 21; page 13, line 27 to page 14, line 20; page 14, line 28 to page 15, line 13. Claim 23 has been amended to recite the isolated nucleic acid molecule of Claim 22 that comprises a nucleic acid sequence having at least 80% sequence identity with nucleotides 1-3419 of SEQ ID NO:1, said identity being determined by using the WU-BLAST-2.0a19 program and calculating the number of matching identical amino acids divided by the sequence length of SEQ ID NO:1. Support for amended claim 23 is found at page 9, line 6 to page 10, line 21 of the specification.

New claims 34-36 have been added. Support for these new claims is found, *inter alia*, at page 5, lines 31-33 and Example 3, pages 44-49.

No new matter is introduced by the amendments to the specification or claims.

A. REJECTION UNDER 35 U.S.C. § 101

Claims 1 and 2 are rejected under 35 U.S.C. § 101, allegedly, as directed to non-statutory subject matter. According to the Examiner, claims 1 and 2 encompass a nematode that is genetically modified. The Examiner states that recitation of a transgenic nematode would be remedial.

Applicants point out that it is believed that from a reading of the specification, and the common usage of the term, one of skill in the art would appreciate that the term "genetically modified" implies that there is human intervention. In any event, claims 1 and 2 have been amended to recite "genetically engineered", which Applicants believe more clearly excludes the possibility of naturally occurring genetic mutations. Applicants appreciate the Examiner's suggestion on how to overcome the rejection, but decline to use the term "transgenic" as the term "genetically engineered" more clearly encompasses genetic manipulations by use of techniques such as RNAi, discussed in the specification at page 22, line 16 to page 23, line 12.

In view of the amendment to claims 1 and 2, Applicants submit that this Section 101 rejection has been obviated, and respectfully request withdrawal of this rejection.

B. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

1. Claims 1-4 and 6-18 are rejected under 35 U.S.C. § 112, first paragraph, allegedly, since the specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention without undue experimentation. According to the Examiner:

> the specification, while being enabling for a transgenic C. elegans whose genome comprises the endogenous csSREBP gene and encodes the amino acid sequence of said csSREBP disclosed in SEQ ID NO 2, wherein said endogenous ceSREBP has been mutated by transposon insertion mutagenesis, wherein said mutation results in a phenotype of early larval arrest, reduced pigmentation as a result of reduced number of lipid droplets in the intestine, and accumulation of fluid filled vesicles, and uses of said transgenic C. elegans, does not reasonably provide enablement for any and all nematodes that have genetically modified expression or mis-expression of any and all SREBP proteins and uses of any and all such genetically modified nematodes.

Applicants respectfully disagree with the Examiner and submit that the claims as amended, and new claims 34-36, fully meet the requirements of Section 112, first paragraph.

Preliminarily, Applicants point out that claim 1 has been amended to recite a *C. elegans* that has been genetically engineered to express or mis-express an SREBP pathway protein selected from the group consisting of SREBP, SCAP, and S2P, or the progeny of said *C. elegans* that has inherited said SREBP pathway protein expression or mis-expression, wherein said SREBP pathway protein expression or mis-expression results in an intestinal defect phenotype, and that claims 2-4, 6, 8-11, 13, 16 and 18 have been amended to specifically recite *C. elegans*.

Applicants submit that the specification provides ample guidance for one of ordinary skill in the art to routinely make and use the claimed genetically engineered *C. elegans*. The Examiner's attention is invited to the specification, *e.g.*, at page 5, line 24 to page 10 which states:

> The use of invertebrate model organism genetics and related technologies can greatly facilitate the elucidation of biological pathways (Scangos, Nat. Biotechnol. (1997) 15:1220-1221; Margolis and Duyk, Nat. Biotechnol. (1998) 16:311). Of particular use are the insect and nematode model organisms, *Drosophila melanogaster*, and *C. elegans*. An extensive search for SREBP pathway nucleic acids and their encoded proteins in *C. elegans* and *Drosophila melanogaster* was conducted in an attempt to identify new and useful tools for probing the function and regulation of the SREBP pathway. Novel SREBP pathway nucleic acids and their encoded proteins are identified herein. As used in this description, the term "SREBP pathway nucleic acid" refers to a nucleic acid that encodes any one of SREBP, SCAP, S1P, and S2P. The newly identified SREBP pathway nucleic acids have led to the discovery of several mutant phenotypes that can be used to study the pathways involved in lipid and fatty acid metabolism.

> The use of invertebrate model organisms such as *Drosophila melanogaster* and *C. elegans* for analyzing the expression and mis-expression of SREBP pathway proteins has great advantages over the traditional approach of using mammalian cell culture due to the ability to rapidly carry out large-scale, systematic genetic screens as well as the ability to screen small molecule libraries directly on whole organisms. Thus, the invention provides a superior approach for identifying other components involved in the synthesis, activation, control and turnover of SREBP pathway proteins. Systematic genetic analysis of the SREBP pathway using invertebrate model organisms can lead to the identification of new drug targets, therapeutic agents, diagnostics and prognostics useful in the treatment of disorders associated with lipid metabolism. Additionally, use of these invertebrate model organisms could lead to the identification and validation of pesticide targets directed to components of the SREBP pathway.

The Examiner's attention is also invited to the specification at page 16, line 27 *et seq.*, wherein methods of identifying or screening for molecules, such as proteins or other compounds, which interact with SREBP pathway proteins, or derivatives, or fragments thereof, are disclosed. Further, the Examiner's attention is invited to Examples 3, 4 and 5, wherein SREBP, SCAP and S2P are mis-expressed in *C. elegans* resulting in a pale intestine phenotype.

With regard to the Examiner's comment on page 4 of the Office Action, as to whether ceSREBP actually functions in the cholesterol synthesis or in fatty acid synthesis pathway, Applicants point out that it is generally accepted in the art that *C. elegans* is unable to synthesize sterols *de novo* and must receive cholesterol, or one of several other sterols, in their diet for sustained growth and reproduction. See, Chitwood, 1999, "Biochemistry and Function of Nematode Steroids", Critical Reviews in Biochemistry and Molecular Biology 34(4):273-284 (a review article citing references prior to the priority date of the above-identified application) (Reference CA, made of record in the Supplemental Information Disclosure Statement submitted herewith). This, in combination with the lipid defects observed in *C. elegans* with mutated SREBP, SCAP, and S2P shown in Examples 3-5, indicates that these genes functions in the fatty acid synthesis pathway.

With regard to the Examiner's comment that *C. elegans* has more than one SREBP homolog, Applicants point out that the *C. elegans* genome has been sequenced [The C. elegans Sequencing Consortium. Genome sequence of the nematode C. elegans: a platform for investigating biology, 1998, Science 282:2012-2018 (Reference CB, made of record in the Supplemental Information Disclosure Statement submitted herewith)] and homology searches of the genomic sequence have not yielded any additional *C. elegans* SREBP genes. This is not surprising, as there are other examples where multiple human

homologues have a single orthologue in *C. elegans*. For example, daf-2, an insulin receptor-like gene that regulates longevity and diapause in *C. elegans*, is 35% identical to the human insulin receptor, 34% identical to the human insulin-like growth factor-I (IGF-I) receptor, and 33% identical to the human insulin receptor-related receptor. Yet, daf-2 is the only member of the insulin receptor family in the *C. elegans* genome. It has been suggested that because daf-2 is equally distant from the human insulin, IGF-I, and insulin receptor-related receptors, it is probably the ortholog of the ancestor of these duplicated and diverged receptors, and thus may subserve any or all of their functions. See, Kimura et al., 1997, Science 277:942-946 (Reference CC, made of record in the Supplemental Information Disclosure Statement submitted herewith).

With regard to the Examiner's comment in the paragraph beginning on the middle of page 5 of the Office Action, whether all the methods of creating genetic modification would have produced transgenic nematodes or *C. elegans* with same phenotype and whether the changes produced would have been inheritable, Applicants note the following. First, claim 1 does not require that the *C. elegans* be transgenic, although transgenics are encompassed by the claim. Further, claim 1 does not require that the intestinal defect phenotype be inheritable and progeny that inherit the intestinal defect phenotype are encompassed by the claim, but progeny that do not inherit the intestinal defect phenotype are not encompassed by the claim. Such features are not needed in order for the genetically engineered worms to have utility in the study of lipid metabolism. For example, as mentioned in the specification, RNAi is a very effective method of gene silencing in *C. elegans*, and can be used as a method of genetic engineering in the present invention. The observed phenotypes for SREBP, S2P and SCAP, while of varying degrees, correlate with each other, and with the general function of SREBP and its pathway members in the fatty acid synthesis pathway. See Examples 3-5 in the present specification. The interference effects of RNAi are manifested in the injected worms and their first generation progeny, but not in future generations. While the genetic modification of a *C. elegans* and its first generation progeny as a result of RNA interference of SREBP pathway genes are important in the present invention, the number of generations for transmittal of an RNA interference phenotype are not relevant. The claims reflect this fact.

The Examiner's comment regarding producing *C. elegans* with the same phenotype on page 5 of the Office Action suggests a need for absolute uniformity in order for the claimed invention to be enabled. However, such uniformity is not legally required. With regard to amended claim 1, which recites that the genetically engineered *C. elegans*

exhibits an intestinal defect phenotype, one skilled in the art will appreciate that different mutations in a given SREBP pathway gene may disrupt that gene's function in varying degrees and will produce intestinal defect phenotypes that differ in severity and penetrance.

The Examiner also questioned whether an SREBP pathway protein that is mutated via different methods such as chemical mutagenesis and insertional mutagenesis would have the same phenotype. In support of his allegation, the Examiner argued that the specification in Example 5 on page 55, line 33 to page 56, line 3 teaches

> that compared to the RNAi method, in the insertional mutagenesis method, about 25% of the heterozygous C. elegans showed the phenotype observed in RNAi method. Which indicates that all the methods may not produce same phenotypes, which may be either due to mutation in different parts of the gene, which may produce different effects on the activity of the protein itself resulting in variable phenotype.

Applicants respectfully submit that the Examiner has misinterpreted the results of Example 5. 25% corresponds to the percentage of progeny of heterozygote SREBP deletion mutants that show the pale intestine phenotype. This presumably correlates to homozygous progeny, given normal Mendelian segregation. As described in Example 5, these progeny have the phenotypes reflective of a modification in an SREBP pathway gene. In any event, it is well within the level of skill in the art to select appropriate genetic modification methods and to screen and select for *C. elegans* that exhibit a pale intestine phenotype, without undue experimentation, which methods are disclosed in the specification.

Applicants submit that one skilled in the art will appreciate that in view of the RNAi and insertional mutagenesis phenotypes described in the specification, it is expected that defects in SREBP pathway genes that result from chemical mutagenesis methods would mimic those observed from other methods. Indeed, subsequent to the filing of the present application, Applicants performed ethylmethane sulfonate (EMS) mutagenesis, phenotypic analysis, and mutation detection (all as described in the specification at pages 20-30), and identified a point mutation in the ceSREBP gene that weakly confers the loss-of-function pale intestine phenotype.

The Examiner's attention is invited to the Declaration of Cynthia Seidel-Dugan under 37 C.F.R. § 1.132 ("the Rule 132 Declaration"). As explained in Paragraph 3 of the Rule 132 Declaration, heterozygous nematodes that carried a partial deletion of ceSREBP (described in Example 5 of the present application) and, in *trans*, a recessive "dumpy (dp)" gene that conferred a short body, were mutagenized. The mutagenized

progeny were screened phenotypically to identify rare individuals that displayed the pale intestine phenotype but not the dumpy phenotype (*i.e.*, genomes carrying SREPB pathway mutation; dp^- over SREBP deletion; dp^+), suggesting that the chromosome carrying the recessive copy of dp now also contained a mutation in a ceSREBP pathway gene, which, in combination with the deletion allele, produced the intestinal defect. Twelve such individuals with the desired phenotype were identified in the initial screen. The progeny of these individuals yielded 8 lines that had a pale intestine and were dumpy. These lines were therefore homozygous for the new EMS induced mutation and the recessive dp allele. In order to eliminate those individuals with mutations in other genes in the pathway and identify mutations specifically in the SREBP gene, these lines were then tested for complementation against the deletion allele of SREBP. One line failed to complement the SREBP deletion allele, demonstrating that it contained a mutation in the ceSREBP gene. Sequence analysis of genomic DNA from the mutant line confirmed the existence of a point mutation that truncated the carboxy-terminal 36 amino acids of the ceSREBP protein in the regulatory domain.

In conclusion, all three methods of genetic modification recited in Claim 2 produce intestinal phenotypes that correlate to modifications in the SREBP pathway genes. Thus, it is within the skill in the art to select a preferred genetic modification method and routinely perform the experiments necessary to select *C. elegans* that fall within the scope of the claims, and thus, the claimed invention can be practiced without undue experimentation.

With regard to the Examiner's allegation that the specification is not enabling for a nematode wherein SREBP protein is expressed using a heterologous protein because the specification has not provided any guidance as to what would have been the effect of the over-expression of SREBP protein on the physiology of the animal and without this information an artisan of skill would not have known how to use such animals, Applicants note the following. Sakai et al. (Reference BW of record) teaches that over-expression of truncated forms of SREBP-2 or SCAP disrupt the complex that forms between full-length SREBP-2 and SCAP. Further, Example 4, beginning on page 49 of the specification describes the overexpression of a dominant negative form of SREBP in *C. elegans* under an inducible heterologous promoter, which results in the pale intestine phenotype. Having been provided by the specification with sequence information for *C. elegans* SREBP, and public domain sequences for SCAP and S2P (see page 44, lines 32-35), that information these genes are members of the fatty acid biosynthesis pathway, and a

detailed description of various intestinal defect phenotypes that result from mutations in the SREBP pathway, *i.e.*, mutation in the SREBP, SCAP and S2P genes, (see, *e.g.*, page 29, lines 15-30), it would be predictable to one skilled in the art that *C. elegans* having modifications in the SREBP, SCAP and S2P genes would have an intestinal defect phenotype. Moreover, one can readily test other over-expression constructs and determine if such results in an intestinal defect phenotype, without undue experimentation.

Regarding claim 6, Applicants respectfully submit that the rejection is not clear. Claim 6, which recites the *C. elegans* of Claim 1 wherein said SREBP pathway protein is encoded by an SREBP pathway nucleic acid sequence linked to a nucleic acid sequence that encodes one or more selectable markers that allows detection of expression of said SREBP pathway protein, does not require the marker gene to indicate "the effect of the gene product on the physiology of the animal or what phenotypes would be produced." Moreover, marker genes and their purpose are described in the specification, *inter alia*, on page 12, lines 29-35; page 18, lines 1-16; page 26, line 33 to page 27, line 2. If the Examiner's point is that certain marker genes may have harmful effects on the animal, rendering some useless, then Applicants' response is that it is well within the level of skill in the art to select appropriate marker genes. If instead, the Examiner's point is that the additional features recited in claim 6 would not cure the enablement rejection as applied to claim 1, such that claim 6 would not be allowable even if written in independent form, then, Applicants incorporate by reference the above remarks that are responsive to the rejection as applied against claim 1. If neither of these arguments is considered responsive, Applicants respectfully request clarification of the rejection of claim 6 in the next Office Action.

With regard to the Examiner's comments on claims 11, 16 and 17, that the specification does not teach or provide any evidence whether pale intestine or intestinal defects would have been observed when any SREBPs would have been disrupted or its expression was inhibited, Applicants note that claim 1, as amended, recites that the SREBP pathway protein is selected from SREBP, S2P and SCAP, and that mutations in each of these proteins resulted in intestinal defects. See, Example 3, beginning on page 44 of the present specification.

In view of the foregoing amendments and remarks, Applicants submit that claims 1-4 and 6, 8-11 and 13-18, as amended, fully meet the requirements of Section 112, first paragraph, and Applicants respectfully request that this Section 112, first paragraph, rejection be withdrawn.

2. Claims 1-4 and 6-11 are rejected under 35 U.S.C. § 112, first paragraph, allegedly, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. According to the Examiner, there is inadequate written description for the nematode genus.

Applicants respectfully disagree with respect to the claims as amended, and point out that in order to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, an Applicant "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." Vas-Cath Inc. v. Mahurkar , 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). For purposes of a 'written description' inquiry, whatever is now claimed by Applicants constitutes the invention. See Vas-Cath at page 1117.

Claims 1 has been amended to recite *C.elegans*, that the SREBP pathway gene is selected from SREBP, S2P, and SCAP, and that the resulting phenotype is an intestinal defect phenotype and claims 2-4 and 6-11 have also been amended to recite *C. elegans*. In view of the amendments to the claims, Applicants respectfully submit that the specification provides a sufficient written description in order to convey to the skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed. Thus, Applicants submit that this Section 112, first paragraph, rejection has been overcome and respectfully request its withdrawal.

3. Claims 22 and 26-28 are rejected under 35 U.S.C. § 112, first paragraph, allegedly, since the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention without undue experimentation. According to the Examiner:

> the specification, while being enabling for a process of producing *C. elegans* SREBP wherein said *C. elegans* SREBP consists of the amino acid sequence disclosed in SEQ ID NO 2 by culturing a host cell that comprises a vector wherein said vector comprises the nucleic acid sequence of SEQ ID NO 1, does not reasonably provide enablement [for] any other embodiment.

Applicants respectfully disagree. Preliminarily, Applicants point out that claim 22 has been amended to recite an isolated nucleic acid molecule of less than 15 kb comprising a nucleic acid sequence that (a) hybridizes to SEQ ID NO:1 under conditions comprising hybridizing in a buffer comprising 6X SSC / 0% formamide at 34°C and washing in a buffer comprising 2X SSC at 45°C, and (b) encodes a functionally active

SREBP polypeptide, said polypeptide having at least 80% sequence identity with amino acids 1-1113 of SEQ ID NO:2, said identity being determined by using the WU-BLAST-2.0a19 program and calculating the number of matching identical amino acids divided by the sequence length of SEQ ID NO:2. Applicants submit that amended claim 22 is fully enabled by the specification. The Examiner's attention is invited to the specification at page 6, line 21 to page 12, which states:

> The invention relates generally to nucleic acid sequences of the SREBP pathway, and more particularly SREBP pathway nucleic acid sequences of *C. elegans* and *Drosophila melanogaster*, and methods of using these sequences. As described in the Examples below, the present invention provides a nucleic acid sequence (SEQ ID NO:1) that was isolated from *C. elegans* and encodes an SREBP homologue referred to herein as "ceSREBP". The invention also provides nucleic acid sequences that were isolated from *Drosophila melanogaster* and encode homologues of S2P (dS2P; SEQ ID NO:3) and SCAP (dSCAP; SEQ ID NO:5). In addition to the fragments and derivatives of SEQ ID NOs 1, 3, and 5, as described in detail below, the invention includes the reverse complements thereof. Also, the subject nucleic acid sequences, derivatives and fragments thereof may be RNA molecules comprising the nucleotide sequence of any one of SEQ ID NOs 1, 3, and 5 (or derivative or fragment thereof) wherein the base U (uracil) is substituted for the base T (thymine). The DNA and RNA sequences of the invention can be single- or double-stranded. Thus, the term "nucleic acid sequence", as used herein, includes the reverse complement, RNA equivalent, DNA or RNA double-stranded sequences, and DNA/RNA hybrids of the sequence being described, unless otherwise indicated explicitly or by context.
>
> Fragments of these sequences can be used for a variety of purposes, for example, as nucleic acid hybridization probes and replication/amplification primers. Certain "antisense" fragments, i.e. that are reverse complements of the sequences set forth in any one of SEQ ID NOs: 1, 3, and 5, have utility in inhibiting the function of SREBP pathway proteins. The fragments are of length sufficient to specifically hybridize with the corresponding SEQ ID NO 1, 3, or 5. In particular, the invention provides fragments of at least 12, preferably at least 24, more preferably at least 36, and more preferably at least 96 contiguous nucleotides of any one of SEQ ID NOs: 1, 3, and 5. In some embodiments, fragments of at least 200 or 500 nucleotides may be preferred. When the fragments are flanked by other nucleic acid sequences, the total length of the combined nucleic acid sequence is less than 15 kb, and preferably less than 10kb, more preferably less than 2 kb, and in some embodiments, more preferably less than 500 bases.

The Examiner's attention is also invited to the specification at page 8, line 13 to page 10, line 21, which describes several exemplary hybridization conditions; to page 13, line 25 to page 14, line 14, which describes methods for determining amino acid sequence similarity

or sequence identity; and to page 14, line 28 to page 15, line 13, which discloses the meaning of "functionally active".

Applicants submit that because of the disclosure of SEQ ID NO:1, SEQ ID NO:2, exemplary hybridization conditions and methods for determining sequence similarity, the specification fully enables the nucleic acids of claim 22, as well as vectors comprising the nucleic acids, host cells comprising the vectors and methods for producing a functionally active SREBP pathway protein having at least 80% sequence identity with amino acids 1-1113 of SEQ ID NO:2, said identity being determined by using the WU-BLAST-2.0a19 program and calculating the number of matching identical amino acids divided by the sequence length of SEQ ID NO:2.

In view of the above amendments and remarks, it is submitted that the specification provides sufficient teaching to allow one skilled in the art to successfully make and use the claimed invention, without undue experimentation. The rejections under Section 112, first paragraph, therefore, should be withdrawn.

C. REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 4, 5, 17 and 23 are rejected under 35 U.S.C. § 112, second paragraph, allegedly, as indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, claim 4 is allegedly vague and indefinite because the term "said promoter" does not have antecedent basis. In response, Applicants have amended claim 4 to recite "said heterologous promoter".

Further, claim 17 is allegedly vague and indefinite for reciting the trademark name BODIPY™. In response, Applicants have amended claim 17 such that the trademark name is no longer recited.

Claim 23 is allegedly vague and indefinite for reciting the term "appropriate". In response, Applicants have amended claim 23 such that the term is no longer recited.

With regard to claim 5, Applicants note that the Examiner has given no reason for its rejection under Section 112, second paragraph; nevertheless, Applicants note that claim 5 has been canceled without prejudice, thus obviating this rejection.

In view of the foregoing, Applicants submit that the Section 112, second paragraph, rejections have been overcome or obviated and respectfully request withdrawal of the rejections under Section 112, second paragraph.

D. REJECTION UNDER 35 U.S.C. § 102(b)

Claims 22-26 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Kohara et al., 1994, Seq Name gb_est47:D35004; Accession No. D35004 (Kohara). According to the Examiner, Kohara discloses a *C. elegans* clone that would encode a polypeptide comprising at least 10 contiguous amino acids of SEQ ID NO:2 or at least 8 contiguous amino acids of residues 335-428 of SEQ ID NO:2, and thus anticipates the invention of claims 22-26.

Applicants respectfully disagree and point out that claim 22 has been amended to recite an isolated nucleic acid molecule of less than 15 kb comprising a nucleic acid sequence that (a) hybridizes to SEQ ID NO:1 under conditions comprising hybridizing in a buffer comprising 6X SSC / 0% formamide at 34°C and washing in a buffer comprising 2X SSC at 45°C, and (b) encodes a functionally active SREBP polypeptide, said polypeptide having at least 80% sequence identity with amino acids 1-1113 of SEQ ID NO:2, said identity being determined by using the WU-BLAST-2.0a19 pathway and calculating the number of matching identical amino acids divided by the sequence length of SEQ ID NO:2. Kohara teaches an EST nucleic acid molecule that encodes a fragment ceSREBP consisting of 109 contiguous amino acids identical to SEQ ID NO:2.

In order for a reference to anticipate a claim, each and every element of the claim must be disclosed in that one reference. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565 (Fed. Cir. 1985). "Anticipation under Section 102 can be found only if a reference shows exactly what is claimed . . ." Structural Rubber Prod. Co. v. Park Rubber Co., 749 F.2d 707 (Fed. Cir. 1984). Kohara cannot and does not anticipate the claimed nucleic acid sequences since Kohara only teaches a nucleic acid that encodes 109 contiguous amino acids identical SEQ ID NO:2; however, Kohara does not teach a functionally active SREBP polypeptide, which polypeptide has at least 80% sequence identity with amino acids 1-1113 of SEQ ID NO:2, said identity being determined by using the WU-BLAST-2.0a19 program and calculating the number of matching identical amino acids divided by the sequence length of SEQ ID NO:2. The Kohara amino acid sequence has only 9.7% sequence identity with SEQ ID NO:2 (109 amino acids out of a total of 1113 amino acids).

Applicants respectfully submit that Kohara does not anticipate the claimed invention, and thus, withdrawal of this Section 102 rejection is respectfully requested.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the file of the above-identified patent application. Claims 1-4, 6, 8-11, 13-18, 22, 23, 25-28 and 34-36 fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejections, allowance and action for issuance are respectfully requested.

Applicants respectfully request that the Examiner call the undersigned at (212) 790-9090 if any questions or issues remain.

Respectfully submitted,

Date: April 6, 2001

Adriane M Antler 32,605

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Enclosures

EXHIBIT A
MARKED VERSION OF AMENDED PARAGRAPH IN THE SPECIFICATION
U.S. PATENT APPLICATION SERIAL NO. 09/332,522
{bracketed text} is deleted and underlined text is added

On page 14, replace the paragraph beginning "A purified derivative" with the following:

A preferred derivative of ceSREBP consists of or comprises an amino acid sequence that has at least 55%, preferably at least 66%, and more preferably, at least 65% sequence identity with amino acid residues 335-428 of SEQ ID NO:2 (i.e. the bHLH-Zip domain). Other preferred derivatives of ceSREBP consist of or comprise an amino acid sequence that shares at least 75% similarity, preferably at least 80% similarity, and more preferably, at least 85% similarity with amino acid residues 335-428 of {SEQ ID NO:1} SEQ ID NO:2. Preferably, such derivatives share antigenicity with amino acid residues 335-428 of {SEQ ID NO:1} SEQ ID NO:2.

EXHIBIT B
MARKED VERSION OF AMENDED CLAIMS
U.S. PATENT APPLICATION SERIAL NO. 09/332,522
[bracketed text is deleted and underlined text is added

1 (once amended). A [animal that is a fly or nematode] *C. elegans* that has been genetically [modified] engineered to express or mis-express an SREBP pathway protein selected from the group consisting of SREBP, SCAP, and S2P, or the progeny of said [animal] *C. elegans* that has inherited said SREBP pathway protein expression or mis-expression, wherein said SREBP pathway protein expression or mis-expression results in an intestinal defect phenotype.

2 (once amended). The [animal] *C. elegans* of Claim 1 that has been genetically [modified] engineered by a method selected from the group consisting of transposon insertion mutagenesis, double-stranded RNA interference, and chemical mutagenesis.

3 (once amended). The [animal] *C. elegans* of Claim 1 wherein a heterologous promoter drives expression or mis-expression of said SREBP pathway protein.

4 (once amended). The [animal] *C. elegans* of Claim 3 wherein said heterologous promoter is selected from the group consisting of tissue-specific promoters, developmental-specific promoters, and inducible promoters.

6 (once amended). The [animal] *C. elegans* of Claim 1 wherein said SREBP pathway protein is encoded by an SREBP pathway nucleic acid sequence linked to a nucleic acid sequence that encodes one or more selectable markers that allows detection of expression of said SREBP pathway protein.

8 (once amended). The [animal] *C. elegans* of Claim 1 wherein said SREBP pathway protein is SREBP and comprises [an] the amino acid sequence [selected from the group consisting of SEQ ID NOs:2, 4, 6, and 8,] of SEQ ID NO:2 or a functionally-active fragment thereof.

9 (once amended). The [animal] *C. elegans* of Claim 8 wherein said SREBP [pathway protein] or functionally active fragment is encoded by [part or all of a] the nucleic acid sequence [selected from the group consisting of SEQ ID NOs:1, 3, 5, and 7] of SEQ ID NO:1, or a fragment thereof.

10 (once amended). The [animal] *C. elegans* of Claim 1 [7 wherein said nematode] that is heterozygous for deletion of SREBP.

11 (once amended). The [animal] *C. elegans* of Claim 1 [7] wherein said [animal is a nematode and said identifiable] intestinal defect phenotype is a pale intestine phenotype [or other intestinal defect].

13 (twice amended). [The method of] A method for studying lipid metabolism comprising obtaining a first *C. elegans* defined by Claim 1 [12] and [additionally comprising observing] a second [animal] *C. elegans* that has the same genetic [modification] engineering as the first [animal] *C. elegans* and that additionally has a mutation in a gene of interest, and detecting a difference [wherein differences, if any,] between the intestinal defect phenotype of the first [animal] *C. elegans* and the intestinal defect phenotype of the second [animal] *C. elegans*, wherein a difference in the phenotypes identifies the gene of interest as capable of modifying the function of the gene encoding said SREBP pathway protein.

15 (once amended). The method of Claim 13 wherein [said animal is a nematode and wherein] said intestinal defect phenotype is a pale intestine phenotype [or other intestinal defect indicative of abnormalities in lipid biosynthesis or metabolism].

16 (once amended). The method of Claim 13 [wherein said animal is a nematode and wherein said method includes] wherein said detecting step comprises staining [said nematode] the first and second *C. elegans in vivo* with a fluorescently-labelled fatty acid conjugate to measure lipid content within said [nematode] first and second *C. elegans*.

17 (once amended). The method of Claim 16 wherein said fluorescently-labelled fatty acid conjugate [is a BODIPY™-fatty acid conjugate] comprises a fatty acid selected from the group consisting of 4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene-3-dodecanoic acid, and 4,4-difluoro-5-methyl-4-bora-3a,4a-diaza-s-indacene-3-dodecanoic acid.

18 (once amended). [The] A method for studying lipid metabolism [of Claim 13 additionally] comprising administering one or more compounds to [said] a *C. elegans* defined by Claim 1 [animal or its progeny]; and observing any changes in lipid content of said *C. elegans* [animal or its progeny].

22 (once amended). An isolated nucleic acid molecule of less than 15 kb comprising a nucleic acid sequence that (a) hybridizes to SEQ ID NO:1 under conditions comprising hybridizing in a buffer comprising 6X SSC / 0% formamide at 34°C and washing in a buffer comprising 2X SSC at 45°C, and (b) encodes a functionally active SREBP polypeptide, said polypeptide having at least 80% sequence identity with amino

acids 1-1113 of SEQ ID NO:2, said identity being determined by using the WU-BLAST-2.0a19 program and calculating the number of matching identical amino acids divided by the sequence length of SEQ ID NO:2 [selected from the group consisting of:

A) a nucleic acid sequence that encodes a SREBP comprising at least 10 contiguous amino acids of the sequence of any one of SEQ ID NO:2, 4 and 6; and

B) a nucleic acid sequence that encodes a polypeptide comprising at least 8 contiguous amino acids of residues 335 to 428 of SEQ ID NO:2].

23 (once amended). The isolated nucleic acid molecule of Claim 22 that [hybridizes under appropriate conditions to] comprises a nucleic acid sequence [selected from the group consisting of SEQ ID NOs:1, 3 and 5] having at least 80% sequence identity with nucleotides 1-3419 of SEQ ID NO:1, said identity being determined by using the WU-BLAST-2.0a19 program and calculating the number of matching identical amino acids divided by the sequence length of SEQ ID NO:2.

EXHIBIT C
PENDING CLAIMS WITH INCORPORATED AMENDMENTS
U.S. PATENT APPLICATION SERIAL NO. 09/332,522

1. A *C. elegans* that has been genetically engineered to express or mis-express an SREBP pathway protein selected from the group consisting of SREBP, SCAP, and S2P, or the progeny of said *C. elegans* that has inherited said SREBP pathway protein expression or mis-expression, wherein said SREBP pathway protein expression or mis-expression results in an intestinal defect phenotype.

2. The *C. elegans* of Claim 1 that has been genetically engineered by a method selected from the group consisting of transposon insertion mutagenesis, double-stranded RNA interference, and chemical mutagenesis.

3. The *C. elegans* of Claim 1 wherein a heterologous promoter drives expression or mis-expression of said SREBP pathway protein.

4. The *C. elegans* of Claim 3 wherein said heterologous promoter is selected from the group consisting of tissue-specific promoters, developmental-specific promoters, and inducible promoters.

6. The *C. elegans* of Claim 1 wherein said SREBP pathway protein is encoded by an SREBP pathway nucleic acid sequence linked to a nucleic acid sequence that encodes one or more selectable markers that allows detection of expression of said SREBP pathway protein.

8. The *C. elegans* of Claim 1 wherein said SREBP pathway protein is SREBP and comprises the amino acid sequence of SEQ ID NO:2 or a functionally-active fragment thereof.

9. The *C. elegans* of Claim 8 wherein said SREBP or functionally active fragment is encoded by the nucleic acid sequence of SEQ ID NO:1, or a fragment thereof.

10. The *C. elegans* of Claim 1 that is heterozygous for deletion of SREBP.

11. The *C. elegans* of Claim 1 wherein said intestinal defect phenotype is a pale intestine phenotype.

13. A method for studying lipid metabolism comprising obtaining a first *C. elegans* defined by Claim 1 and a second *C. elegans* that has the same genetic engineering as the first *C. elegans* and that additionally has a mutation in a gene of interest, and detecting a difference between the intestinal defect phenotype of the first *C. elegans* and the intestinal defect phenotype of the second *C. elegans*, wherein a difference in the phenotypes

identifies the gene of interest as capable of modifying the function of the gene encoding said SREBP pathway protein.

14. The method of Claim 13 wherein said gene of interest is implicated in cholesterol or fatty acid biosynthesis.

15. The method of Claim 13 wherein said intestinal defect phenotype is a pale intestine phenotype.

16. The method of Claim 13 wherein said detecting step comprises staining the first and second *C. elegans in vivo* with a fluorescently-labelled fatty acid conjugate to measure lipid content within said first and second *C. elegans*.

17. The method of Claim 16 wherein said fluorescently-labelled fatty acid conjugate comprises a fatty acid selected from the group consisting of 4,4-difluoro-5,7-dimethyl- 4-bora-3a,4a-diaza-s-indacene-3-dodecanoic acid, and 4,4-difluoro-5-methyl-4-bora-3a,4a-diaza-s-indacene-3-dodecanoic acid.

18. A method for studying lipid metabolism comprising administering one or more compounds to a *C. elegans* defined by Claim 1; and observing any changes in lipid content of said *C. elegans*.

22. An isolated nucleic acid molecule of less than 15 kb comprising a nucleic acid sequence that (a) hybridizes to SEQ ID NO:1 under conditions comprising hybridizing in a buffer comprising 6X SSC / 0% formamide at 34°C and washing in a buffer comprising 2X SSC at 45°C, and (b) encodes a functionally active SREBP polypeptide, said polypeptide having at least 80% sequence identity with amino acids 1-1113 of SEQ ID NO:2, said identity being determined by using the WU-BLAST-2.0a19 program and calculating the number of matching identical amino acids divided by the sequence length of SEQ ID NO:2.

23. The isolated nucleic acid molecule of Claim 22 that comprises a nucleic acid sequence having at least 80% sequence identity with nucleotides 1-3419 of SEQ ID NO:1, said identity being determined by using the WU-BLAST-2.0a19 program and calculating the number of matching identical amino acids divided by the sequence length of SEQ ID NO:1.

25. A vector comprising the nucleic acid molecule of Claim 22.

26. A host cell comprising the vector of Claim 25.

27. The host cell of Claim 26 wherein said cell is a yeast cell.

28. A process for producing an SREBP pathway protein comprising culturing the host cell of Claim 26 under conditions suitable for expression of said SREBP pathway protein and recovering said protein.

34. The *C. elegans* of Claim 1 that has been genetically engineered to express or mis-express SREBP.

35. The *C. elegans* of Claim 1 that has been genetically engineered to express or mis-express SCAP.

36. The *C. elegans* of Claim 1 that has been genetically engineered to express or mis-express S2P.

#12
KD
4-18-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Costa et al.	Group Art Unit: 1632
Serial No.: 09/332,522	Examiner: R. Shukla
Filed: June 14, 1999	Attorney Docket No: 7326-101
For: ANIMAL MODELS AND METHODS FOR ANALYSIS OF LIPID METABOLISM AND SCREENING OF PHARMACEUTICAL AND PESTICIDAL AGENTS THAT MODULATE LIPID METABOLISM	

DECLARATION OF CYNTHIA SEIDEL-DUGAN UNDER 37 C.F.R. § 1.132

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

I, CYNTHIA SEIDEL-DUGAN, do declare and state:

1. I am presently the program leader for Metabolic Disease at Exelixis, Inc., assignee of the above-identified application, serial number 09/332,522 ("the '522 application"). The experiments described on pages 44 through 50 of this application, as well as experiments related to SREBP following the filing of this application, described in paragraph 3 below, have been carried out under my direction and supervision.

2. My academic and industrial experience, honors, and list of publications are set forth in my *curriculum vitae*, attached hereto as **Exhibit 1**.

3. I have read and am familiar with the '522 application and the October 6, 2000 Office Action. I understand that the Examiner has rejected claims 1-4 and 6-18 under 35 U.S.C.§ 112, first paragraph, for alleged lack of enablement. Specifically, the Examiner questions whether all methods of producing transgenic nematodes would lead to the same phenotype. More specifically, the Examiner questions whether a *C. elegans* having a mutation in the SREBP pathway, produced by chemical mutagenesis, would have the same phenotype as worms having a mutation in the SREBP pathway produced using RNAi and transposon insertional mutagenesis, as described in the present application, in Examples 3-5. Since filing of the instant application, using methods of ethyl methane sulfonate (EMS) mutagenesis, phenotypic analysis, and mutation detection (all as described in the specification at pages 20-30), we identified a point mutation in the ceSREBP gene that confers the loss-of-function pale intestine phenotype. Briefly, 9500 heterozygous worms were used in a chemical mutagenesis screen. The parental worm strain was heterozygous for two mutations: a partial deletion of ceSREBP, described in detail in Example 5 of the '522 application, and a dominant copy of the tightly linked dumpy (dp) gene. Thus, each worm carried, in trans, a normal copy of the ceSREBP and a recessive copy of the dp gene. The dumpy (dp) gene, used as a marker, confers a short body when homozygous recessive. The worms were mutagenized using EMS chemical mutagenesis in order to isolate potential mutations in the ceSREBP gene. The mutagenized progeny were screened phenotypically to identify rare individuals that displayed the pale intestine phenotype but not the dumpy phenotype (i.e., genomes carrying SREPB pathway mutation; dp^- over SREBP deletion; dp^+), suggesting that the chromosome carrying the recessive copy of dp now also contained a mutation in a ceSREBP pathway gene, which, in combination with the deletion allele, produced the intestinal defect. Twelve such individuals with the desired phenotype were identified in the initial screen. The progeny of these individuals yielded 8 lines that had a pale intestine and were dumpy. These lines were therefore homozygous

for the new EMS induced mutation and the recessive dp allele. In order to eliminate those individuals with mutations in other genes in the pathway and identify mutations specifically in the SREBP gene, these lines were then tested for complementation against the deletion allele of SREBP. One line failed to complement the SREBP deletion allele, demonstrating that it contained a mutation in the ceSREBP gene. Sequence analysis of genomic DNA from the mutant line confirmed the existence of a point mutation that truncated the carboxy-terminal 36 amino acids of the ceSREBP protein in the regulatory domain. Accordingly, the above results unambiguously demonstrate that chemical mutagenesis can generate mutant worms with the same phenotype (pale intestine) as those generated by RNAi or insertional mutagenesis.

4. I declare further that all statements made in this declaration of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: April 6, 2001 By: _____
Cynthia Seidel-Dugan

Attachment:

Exhibit 1: *Curriculum Vitae* of Cynthia Seidel-Dugan

Cynthia Seidel-Dugan, Ph.D.
1755 Ellie Court
Benicia, CA 94510
707-748-4383

PROFESSIONAL EXPERIENCE

EXELIXIS Inc., South San Francisco, CA

Senior Research Scientist II, Program Leader Metabolic Diseases 1999 to present
Senior Research Scientist, Molecular Target Research 1997-1999
Group Leader - Assay Development, 1995 to 1997.

1998-present
Program Leader for the Metabolic Diseases Program in collaboration with Pharmacia Corporation. Responsible for managing a team of 19 scientists utilizing model organism genetics to identify novel therapeutic targets for the treatment of Type 2 Diabetes. Project includes studies of the insulin receptor (InR) and SREBP signaling pathways in *C. elegans* and *Drosophila* melanogaster. Nine candidate target genes have been accepted by our corporate partner, generating milestones. Served as a member of the Joint Scientific Committee to oversee program progress and set research goals.

1995-1997
Established a research group to develop cell-based assays for target identification and lead compound discovery. Responsibilities also include expression and purification of recombinant proteins, establishment of assays to examine the functional activity of these proteins, polyclonal and monoclonal antibody production.

Principal Investigator for a research project examining the therapeutic value of neuronal chemoattractant and chemorepellent molecules. Optimization of mammalian expression systems for producing recombinant proteins to be used as antigens for antibody production and in functional assays for axonal outgrowth from spinal cord explant cultures. Established outside collaborations to examine the activity of these molecules in several model systems: a. animal models of nerve regeneration and b. *in vitro* assays of immune cell function. Submitted an SBIR grant proposal entitled 'Semaphorins as novel chemokines' in August, 1996.

ARIAD Pharmaceuticals Inc., Cambridge, MA.
Senior Research Scientist, 1992 to 1995

Coordinator of the cell-based assay group. Member of the Allergy/Asthma and Immune Response Project Teams. Responsibilities included development of cell-

based assays to determine potency and toxicity of compounds in the drug discovery program, supervision of personnel dedicated to running the assays, data analysis and presentation of results to the project team. Assays were designed to measure early as well as late events following receptor stimulation in mast cell and human T cell lines, including changes in phorphorylation states of multiple cellular targets. Established a human basophil assay and a model system for examining human mast cells prepared from umbilical cord blood. Developed *in vitro* tyrosine kinase assays.

Principal investigator for a research project examining early signal transduction events in mast cells following stimulation of the high affinity IgE receptor FcεRI. Model systems utilized include SLO-permeabilized RBL cells to study the role of the Syk tyrosine kinase and construction/expression of CD8/FcεRI receptor chimeric molecules to characterize the molecular events leading to receptor activation. Focus of the work was the identification of key steps in the signaling pathway leading to functional activation of the mast cell, and incorporating this information into assays designed to determine target specificity.

Research Technician, Children's Hospital of Philadelphia, Philadelphia, PA.
1980 to 1984.

Characterization of HSV gC as a C3b receptor, also involved in serological studies of a trial human cytomegalovirus vaccine. Techniques employed include cell culture, virus cultivation and infectivity assays, viral neutralization assays.

EDUCATION

Postdoctoral Fellow, Department of Microbiology, University of Pennsylvania, Philadelphia, PA. 1990 to 1992.
Advisor: Joan S. Brugge, Ph.D.

Structure and function studies of SH2 and SH3 domains of the protein tyrosine kinase Src; characterization of the role of Src SH2 and SH3 domains in transformation of chicken embryo fibroblasts; identification of protein interactions dependent on SH2 and SH3 domains. Techniques employed include cloning, site-directed mutagenesis, DNA sequencing, cell culture and transfection, immunofluorescence, immunoprecipitations, phosphopeptide mapping, *in vitro* kinase assays, SDS-PAGE, anti-phosphotyrosine immunoblotting, bacterial expression and purification of fusion peptides.

Graduate student, Program in Microbiology, Molecular Biology Graduate Group, University of Pennsylvania, Philadelphia, PA. 1984 to 1990.
Advisors: Gary H. Cohen, Ph. D. and Roselyn J. Eisenberg, Ph.D.

Dissertation: Structure and function of Herpes simplex virus glycoprotein C as a receptor for C3b fragment of complement. Analysis of the structure and function of glycoprotein C of HSV types 1 and 2; identification of regions in gC important for C3b receptor activity; characterization of the gC/C3b interaction. Techniques employed include cloning, site-directed mutagenesis, DNA sequencing, Southern blotting, cell culture, transfection of mammalian cells, immunofluorescence, SDS-PAGE, immunoblotting, protein purification, production and characterization of polyclonal and monoclonal antibodies.

College of William and Mary, Williamsburg, VA
BS in Biology, 1980

FELLOWSHIPS AND AWARDS

9/84 to 6/87 NIH Predoctoral Traineeship, Cell and Molecular Biology Training Grant.

7/87 to 12/89 NIH Predoctoral Traineeship, Virology Training Grant.

ACADEMIC SERVICE

1986 to 1987. Graduate student representative to the Executive Committee, Microbiology Graduate Group.

1987 to 1989. Graduate student representative to the Program Committee in Microbiology, Molecular Biology Graduate Group.

INVITED SPEAKER

Nutritional Control of Gene Transcription, October 22-25, 1999 Taos, New Mexico, "Invertebrate genetics as a tool for target identification in the insulin signaling pathway".

PUBLICATIONS

Xu X, Ng S, Wu ZL, Nguyen D, Homburger S, Seidel-Dugan C, Ebens A, Luo Y. 1998. Human semaphorin K1 is glycosylphosphatidylinositol-linked and defines a new subfamily of viral-related semaphorins. J Biol Chem 273:22428-34.

Taylor, J.A., J.L. Karas, M.K. Ram, O.M. Green and C. Seidel-Dugan. 1995. Activation of the high-affinity immunoglobulin E receptor FcεRI in RBL-2H3 cells is inhibited by Syk SH2 domains. Mol. Cell. Biol. 15:4149-4157.

Weng, Z., S.M. Thomas, R.J. Rickles, J.A. Taylor, A.W. Brauer, C. Seidel-Dugan, W.M. Michael, G. Dreyfuss and J.S. Brugge. 1994. Identification of Src, Fyn, and Lyn SH3-binding proteins: implications for a function of SH3 domains. Mol. Cell. Biol. 14: 4509-4521.

Weng, Z., J.A. Taylor, C.E. Turner, J.S. Brugge and C. Seidel-Dugan. 1993. Detection of Src homology 3-binding proteins, including paxillin, in normal and v-src-transformed Balb/c 3T3 cells. J. Biol. Chem. 268: 14956-14963.

Yu H, Rosen MK, Shin TB, Seidel-Dugan C, Brugge JS, Schreiber SL. 1992. Solution structure of the SH3 domain of Src and identification of its ligand-binding site. Science 258:1665-8

Seidel-Dugan, C., B.M. Meyer, S.M. Thomas and J.S. Brugge. 1992. The effects of SH2 and SH3 deletions on the functional activity of wild-type and transforming variants of c-Src. Mol. Cell. Biol. 12:1835-1845.

Ruth Tal-Singer, C. Seidel-Dugan, L. Fries, H.P. Huemer, R.J. Eisenberg, G.H. Cohen and H.M. Friedman. 1991. Herpes simplex virus glycoprotein C is a receptor for complement component iC3b. J. Infect. Dis. 164: 750-753.

Seidel-Dugan, C., M. Ponce de Leon, H.M. Friedman, Roselyn J. Eisenberg, and Gary H. Cohen. 1990. Identification of C3b-binding regions on herpes simplex virus type 2 glycoprotein C. J. Virol. 64: 1897-1906.

Friedman, H.M., A. Yee, H. Diggelmann, J. Hastings, R. Tal-Singer, C.Seidel-Dugan, R.J. Eisenberg and G.H. Cohen. 1989. Use of glucocorticoid-inducible promoter for expression of herpes simplex virus type 1 glycoprotein C1, a cytotoxic protein in mammalian cells. Mol. Cell. Biol. 9: 2303-2314.

Seidel-Dugan, C., M. Ponce de Leon, H.M. Friedman, L.F. Fries, M.M. Frank, G.H. Cohen and R.J. Eisenberg. 1988. C3b receptor activity on transfected cells expressing glycoprotein C of herpes simplex virus types 1 and 2. J. Virol. 62: 4027-4036.

Friedman, H.M., G.H.Cohen, R.J. Eisenberg, C.A. Seidel and D.B. Cines. 1984. Glycoprotein C of herpes simplex virus 1 functions as a C3b receptor on infected endothelial cells. Nature (London) 309: 633-635.

ABSTRACTS

Taylor, J.A., J.L. Karas, M.K. Ram, O.M. Green and C. Seidel-Dugan. 1995. Activation of the high affinity IgE receptor FcεRI in RBL-2H3 cells is inhibited by Syk SH2 domains. Second International Workshop on Signal Transduction in Mast Cell Activation and Development. Bethesda, MD.

Weng, Z., J.A. Taylor, J.S. Brugge and C. Seidel-Dugan. 1992. Identification of SH3 binding proteins in normal and v-Src transformed BALB/3T3 cells. Eighth Annual Meeting on Oncogenes, Frederick, MD.

Seidel-Dugan, C., B.E. Meyer, S.M. Thomas and J.S. Brugge. 1991. The SH2 and SH3 homology domains of $pp60^{src}$ are not required for transformation of chicken embryo fibroblasts. Seventh Annual Meeting on Oncogenes. Frederick, MD.

Seidel-Dugan, C., S.M. Thomas, S. Halegoua and J.S. Brugge. 1990. Comparison of the effects of NGF, *v-src*, and mutant variants of *src* on neuronal differentiation in PC12 cells. Sixth Annual Meeting on Oncogenes, Frederick, MD.

Seidel-Dugan, C., T.J. Tucker, M. Ponce de Leon, H.M. Friedman, G.H. Cohen and R.J. Eisenberg. 1988. Identification of C3b binding domains in HSV-2 glycoprotein C. 13th International Herpesvirus Workshop, University of California, Irvine.

Seidel-Dugan, M.Ponce de Leon, H.M. Friedman, G.H. Cohen and R.J. Eisenberg. 1987. Expression of HSV glycoprotein C in mammalian cells and analysis of C3b binding domains. 12th International Herpesvirus Workshop, Philadelphia, PA.

Friedman, H.M., A. Yee, H. Diggelmann, C. Seidel-Dugan, G. Cohen and R.J. Eisenberg. 1987. Stable expression of HSV-1 glycoprotein C in mammalian cells under the control of an inducible promoter. 12th International Herpesvirus Workshop, Philadelphia, PA.

Seidel-Dugan, C., M. Ponce de Leon, H.M. Friedman, G.H. Cohen and R.J. Eisenberg. 1987. Expression of HSV glycoprotein C in mammalian cells and analysis of C3b binding domains. Sixth Annual Meeting of the American Society for Virology.

Friedman, H.M., G. Cohen, R. Eisenberg, C. Seidel and D. Cines. 1983. Glycoprotein C of HSV-1 functions as a receptor for the complement component C3b. International Herpes Virus Workshop, Oxford, England.

Smiley, L., C. Seidel and H.M. Friedman. 1983. Glycoprotein C of herpes simplex virus type 1 functions as a C3b receptor. American Federation for Clinical Research.

Friedman, H.M., C.Seidel and D.B. Cines. 1982. Characterization of the C3 receptor of herpes simplex virus type 1. American Federation for Clinical Research.